

CLAIMS

1. A microcapsule for the modified release of at least one AP with low solubility, intended to be
5 administered orally and of the type of those:

- each consisting of a core comprising at least one active principle and of a coating film applied onto the core and controlling the modified release of the AP(s),
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- the mean diameter of which is less than 1000 microns, preferably between 800 and 50 microns, and even more preferably between 600 and 100 microns,
- in which the coating film of each micro-
15 capsule contains the following components:
 - -I-- at least one film-forming polymer (P1) insoluble in gastrointestinal tract fluids,
 - -II-- at least one water-soluble polymer (P2),
 - -III- at least one plasticizer (PL),
 - -IV- and, optionally, at least one lubricating surfactant (TA);

characterized in that:

- 25 ➤ their coating film represents at least 3% dry weight/dry weight, preferably at least 5% dry weight/dry weight of their total mass,
- 30 ➤ and their core contains at least one AP and at least one solubilizing agent having the particularity, as soon as it is placed in aqueous solution at a concentration of 20% w/w at 37°C, of increasing the solubility of the AP by more than 50%.

35 2. The microcapsule as claimed in claim 1, characterized in that the components P1, P2 and PL of the coating film satisfy the following characteristics:

- mass fraction by dry weight of P1 relative

to the total mass of the coating of between 40 and 90%, and preferably of between 50 and 80%;

- 5 ■ mass fraction by dry weight P_2/P_1+P_2 of between 15 and 60%, and preferably of between 15 and 55%;
 - mass fraction by dry weight P_L/P_1+P_L of between 1 and 30%, and preferably of between 5 and 25%.
- 10 3. The microcapsule as claimed in claim 1 or 2, characterized in that the coating film comprises component TA in a proportion of 2 and 20%, and preferably of between 4 and 15% of the total mass of the dry coating.
- 15 4. The microcapsule as claimed in claim 1 or 3, characterized in that the solubilizing agent(s) present in the core with the AP confer(s), on the core in which it (they) is (are) included, properties such that the behavior of the exposed (non-coated) core in a given 20 dissolving test TD is as follows: release of 80% of the AP in less than two hours, preferably in less than one hour.
5. The microcapsule as claimed in any one of claims 1 to 4, characterized in that the solubilizing 25 agent is chosen from the following families:
(a) hydrophilic polymers, preferably:
 - polyvinyl pyrrolidone,
 - polyvinyl alcohol,
 - hydrophilic derivatives of cellulose, preferably hydroxypropylcellulose and/or carboxymethylcellulose,
 - maltodextrins,
 - polyethylene glycol (PEG);

- 30 (b) surfactants, preferably:
 - polyoxyethylene-polyoxypropylene copolymers,
 - polyoxyethylenated hydrogenated castor oil,
 - sodium dodecyl sulfate,
 - esters of sucrose and of sorbitan,
 - phospholipids,

- polyethylene glycol (PEG) stearate,
- disodium pamoate,
- polyoxyethylenated oils,
- polysorbates;

5 (c) or else from sequestering agents, preferably cyclodextrins;
(d) and mixtures thereof.

6. The microcapsule as claimed in any one of claims 1 to 5, characterized in that the mass fraction 10 [solubilizing agent] × 100/[solubilizing agent + AP] is greater than or equal to 5%, and preferably between 10 and 98%.

7. The microcapsule as claimed in any one of claims 1 to 6, characterized in that P1 is selected from 15 the group of products below:

- water-insoluble derivatives of cellulose, preferably ethylcellulose and/or cellulose acetate,
- acrylic derivatives,
- poly(vinyl acetates),
- and mixtures thereof.

8. The microcapsule as claimed in any of one of claims 1 to 7, characterized in that P2 is selected from the group of products below:

- 25 • water-soluble derivatives of cellulose,
- polyacrylamides,
- poly-N-vinylamides,
- poly(N-vinyl lactams),
- polyvinyl alcohols (PVAs),
- 30 • polyoxyethylenes (POEs),
- polyvinylpyrrolidones (PVPs) (the latter being preferred),
- and mixtures thereof.

9. The microcapsule as claimed in any one of 35 claims 1 to 8, characterized in that PL is selected from the group of products below:

- glycerol and esters thereof, preferably from the following subgroup:
acetylated glycerides, glyceryl mono-

- stearate, glyceryl triacetate, glyceryl tributylate,
- phthalates, preferably from the following subgroup:
 - 5 dibutyl phthalate, diethyl phthalate, dimethyl phthalate, dioctyl phthalate,
 - citrates, preferably from the following subgroup:
 - 10 acetyl tributyl citrate, acetyl triethyl citrate, tributyl citrate, triethyl citrate,
 - sebacates, preferably from the following subgroup:
 - 15 diethyl sebacate, dibutyl sebacate,
 - adipates,
 - azelates,
 - benzoates,
 - plant oils,
 - fumarates, preferably diethyl fumarate,
 - malates, preferably diethyl malate,
 - 20 • oxalates, preferably diethyl oxalate,
 - succinates, preferably dibutyl succinate,
 - butyrates,
 - cetyl alcohol esters,
 - salicylic acid,
 - 25 • triacetin,
 - malonates, preferably diethyl malonate,
 - cutin,
 - castor oil (this being particularly preferred),
 - 30 • and mixtures thereof.
10. The microcapsule as claimed in any one of claims 1 to 9, characterized in that TA is selected from the group of products below:
- 35 • anionic surfactants, preferably from the subgroup of alkali metal salts or alkaline-earth metal salts of fatty acids, stearic acid and/or oleic acid being preferred,
 - and/or nonionic surfactants, preferably from the following subgroup:

- o polyoxyethylenated oils, preferably polyoxyethylenated hydrogenated castor oil,
- o polyoxyethylene-polyoxypropylene copolymers,
- 5 o polyoxyethylenated sorbitan esters,
- o polyoxyethylenated castor oil derivatives,
- o stearates, preferably calcium stearate, magnesium stearate, aluminum stearate or zinc stearate,
- 10 o stearyl fumarates, preferably sodium stearyl fumarate,
- o glyceryl behenate,
- o and mixtures thereof.

11. The microcapsule as claimed in any one of
15 claims 1 to 10, characterized in that the APs with low
solubility are chosen from at least one of the major
varieties of active substances below:

antiulcer agents, antidiabetic agents, anticoagulants,
antithrombics, blood lipid-lowering agents, anti-
20 arrhythmics, vasodilators, antiangina agents, anti-
hypertensives, vasoprotective agents, fertility
promoters, inducers and inhibitors of uterine labor,
contraceptives, antibiotics, antifungal agents, anti-
viral agents, anticancer agents, anti-inflammatory agents,
25 analgesics, antiepileptics, antiparkinsonian agents,
neuroleptics, hypnotics, anxiolytics, psychostimulants,
antimigraine agents, antidepressives, antitussives,
antihistamines or antiallergic agents.

12. The microcapsule as claimed in claim 11,
30 characterized in that the AP(s) with low solubility is
(are) chosen from the following compounds: prazosine,
acyclovir, nifedipine, naproxen, ibuprofen, ketoprofen,
fenoprofen, indomethacine, diclofenac, sulpiride,
terfenadine, carbamazepine, fluoxetine, alprazolam,
35 famotidine, ganciclovir, spironolactone,
acetylsalicylic acid, quinidine, morphine,
amoxicillin, paracetamol, metoclopramide, verapamil and
mixtures thereof.

13. A medicinal product comprising the micro-

capsules as claimed in any one of claims 1 to 12.

14. The medicinal product as claimed in claim 13, characterized in that it is in solid form, preferably: tablet, gelatin capsule or powder, or in liquid form, 5 preferably: an aqueous suspension.

15. The use of microcapsules:

- each consisting of a core comprising at least one active principle and of a coating film applied onto the core and controlling the prolonged release of the AP(s),
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- the mean diameter of which is less than 1000 microns, preferably between 800 and 50 microns, and even more preferably between 600 and 100 microns,
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- in which the coating film of each micro-capsule contains the following components:
 - -I-- at least one film-forming polymer (P1) insoluble in gastrointestinal tract fluids,
 - -II-- at least one water-soluble polymer (P2),
 - -III- at least one plasticizer (PL),
 - -IV- and, optionally, at least one lubricating surfactant (TA);

25 characterized in that:

- their coating film represents at least 4% dry weight/dry weight, preferably at least 5% dry weight/dry weight of their total mass,
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 - and their core contains at least one AP and at least one solubilizing agent having the particularity, as soon as it is placed in aqueous solution at a concentration of 20% w/w at 37°C, of increasing the solubility of the AP by more than 50%,
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- for producing a medicinal product based on at least one AP with low solubility which can be administered orally, which can be readily swallowed, and which is released in vivo in a controlled, prolonged and,

optionally, delayed manner.